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Systematic Review and Meta-analysis of Vagus Nerve Stimulation in the Treatment of Heart Failure

Cristina FURNICA[1], Raluca Ozana CHISTOL[2]*, Mihaela GRECU[3], Mihaela TOMAZIU-TODOSIA[4], Grigore TINICA[5]

Abstract

The vagus nerve, the longest cranial nerve, mixed, with both motor and sensitive components, innervates the structures derived from the last two pharyngeal arches and constitutes the main efference of the cranial parasympathetic system, presenting the widest distribution in the human body. Vagus nerve dysfunction is encountered in several cardiac diseases including atrial fibrillation (AFib) and heart failure. Vagus nerve stimulation (VNS) may slow or cancel pathophysiological processes involved in heart failure development. The aim of the current study was to perform a meta-analysis of the available data obtained in a clinical setting for VNS in heart failure patients in order to establish a potential benefit in terms of cardiac function. The authors performed a systematic review and meta-analysis of available data published between January 2010 - April 2017 by searching the Medline database using "vagus nerve stimulation" and "heart failure" as keywords. From 116 identified studies, only 4 met the inclusion criteria after abstract analysis. The four identified studies (2 randomized, 2 non-randomized) evaluated the effect of VNS in patients ≥18 years-old with

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NYHA functional class II-III heart failure due to various causes and reduced left ventricular ejection fraction. The two randomized trials failed to demonstrate a significant improvement of mortality rate, functional remodelling or functional capacity in symptomatic heart failure patients compared to the two non-randomized trials that displayed promising results on small and biased study groups. Their observed benefits in quality of life have to be interpreted with caution given the subjective nature and lack patient blindness. In conclusion, prior to new clinical studies, the specific site, intensity and duration of adequate stimulation should be identified together with a method of isolating the efferent vagal fibres in order to avoid cross-stimulation and side-effects.

Keywords: atrial fibrillation, heart failure, vagus nerve stimulation, NYHA class.

1. Introduction

The **vagus nerve (CNS X, pneumogastric nerve)**, the longest cranial nerve, mixed, with both motor and sensitive components, innervates the structures derived from the last two pharyngeal arches and constitutes the main efference of the cranial parasympathetic system, presenting the widest distribution in the human body. Morphologically, the vagus nerve contains somatic and visceral afferent fibers, general and special visceral efferent fibers.

The **motor component** consists of [5]:

- special visceral efferent fibres (SVE) distributing to the derivatives of the mesenchyme of the fourth (pharyngeal muscles) and sixth (larynx and superior oesophagus muscle) pharyngeal arches;
- general **n. X** visceral efferent fibres (GVE) represented by preganglionic parasympathetic axons that distribute to and synapse in the intraparietal microganglionic systems of the thoracoabdominal viscera, except the left colon and the pelvic organs.

The **sensitive component** consists of [5]:

- general visceral afferent fibres (GVA) from the retroauricular, external acoustic meatus and external tympanic integument;
- special visceral afferent fibres (SVA) from the taste receptors located at the base of the tongue and on the anterior face of the epiglottis, as well as from the aortic arch and atrial chemoreceptors and baroreceptors;
- general visceral afferent fibres (GVA) that are peripheral afferent axons of the inferior ganglion neurons, synapse with the organofugal neurons of the intraparietal microganglionic plexuses of the thoracoabdominal viscera and carry all the visceral sensibility information, except the nociception.

The real origin

The special visceral efferent fibres (SVE) originate in the ***ambiguus nucleus***, shaped as a neuronal column located in the depth of the medulla reticular formation between a caudal plane through the lemniscal decussation and a rostral plane corresponding to the middle third of the inferior olivary complex [2].

The general visceral efferent fibres (GVE) originate in the **dorsal nucleus of the vagus nerve** is situated under the floor of the IVth ventricle, in the medial part of the *vagal trigonum (ala cinerea)* between the solitary fascicle, laterally, and *the hypoglossus nucleus,* medially, from which is separated by the intercalated nucleus [5].

Cardiac fibres originate mainly in the ***ambiguus nucleus*** and to a lesser extent the solitary nucleus.

The general somatic afferent fibres (GVA) from the retroauricular, external acoustic meatus and external tympanic integument originate in the **superior ganglion** (jugular), located anteromedially to the jugular ligament, into the nervous compartment (*pars nervosa*) of the jugular foramen. The central axons enter the medulla through the retroolivary groove and participate to the formation of the spinal trigeminal tract and synapse in the dorsal part of the trigeminal spinal nucleus [5].

The general visceral afferent fibres (GVA) originate in the **inferior ganglion** that is fusiform shaped, 1-2 cm long, and overpasses inferiorly the jugular foramen in order to enter the neurovascular sheath of the neck. It is partially fused or connected through communicating branches with the superior sympathetic cervical ganglion. The peripheral axons of the inferior ganglion pseudounipolar neurons carry information concerning the reflex activity of the cardiovascular, respiratory and digestive systems. This information could be *direct*, from the aortic arch baroreceptors, aortic arch glomus chemoreceptors or *indirect*, from organofugal neurons belonging to the intraparietal nervous systems of thoracoabdominal viscera [5].

The special visceral afferent fibres (SVA) also originate in the inferior ganglion, and the peripheral axons of the pseudounipolar local neurons carry taste information from the base of the tongue and epiglottis.

Central axons of the general visceral sensibility and special sensibility enter the medulla through the retroolivary groove, participating to solitary tract formation and synapse in the solitary nucleus, a neural column centred by the solitary tract and located under the floor of the IVth ventricle, on the lateral part of *ala cinerea*.

The solitary nucleus is intimately interconnected with *area postrema*, the most distal circumventricular organ located on the inferolateral margin

of the floor of the IVth ventricle. The *area postrema* contains angiotensin and atrial natriuretic peptide receptors involved in cardiovascular regulation (blood pressure, liquids intake) via the vagus nerve [5].

The ventrolateral medulla consisting of reticulospinal neuronal groups, cardiovagal and propriomedullary neurons is intimately interconnected with the solitary nucleus. ***The rostral ventrolateral medulla*** is the stimulatory centre of the precardiac sympathetic neurons from the lateral horn of the spinal cord and its stimulation increases the heart rate, blood pressure, catecholamine release from the adrenal gland medulla as well as from its own catecholaminergic C1 group. ***The caudal ventrolateral medulla*** is the antagonist depressor centre which contains sympathetic inhibitory neurons who, following activation by impulses from solitary nucleus barosensitive neurons, induce hypotension and bradycardia [5].

Respiratory and cardiovascular activity are coordinated by the chemosensitive central area consisting of chemoreceptors superficially disseminated on the ventrolateral face of the medulla and activated by CO_2 partial pressure increase and pH decrease.

The superficial origin

The vagus nerve emerges as 8-10 roots through the middle part of the medullar retroolivary sulcus, between the origins of the glossopharyngeal and accessory nerves.

The roots converge and form a unique trunk with an 8-9 mm long intracisternal course. The vagus nerve crosses the inferior part of the pontocerebellar angle, then engages into the vagal pore of the jugular foramen. CNS X leaves the skull through the middle compartment of the jugular foramen, where it has upper and lower ganglionic swellings, the sensory ganglia of the nerve. The superior ganglion (jugular) is less than 0.5 cm in diameter, while the inferior (nodose) ganglion is larger (2.5 cm) and lies 1 cm distal to the superior ganglion. Below the inferior ganglion the vagus nerve is joined by the cranial root of the accessory nerve (cranial nerve XI).

Extracranially, the vagus nerve descends vertically within the carotid sheath posterolateral to the internal and common carotid arteries and medial to the internal jugular vein (IJV) at the root of the neck. The **extracranial course** could be divided into *deep facial*, *cervical, superior mediastinal*, *inferior mediastinal* and *abdominal segments* [2,5].

In the **deep facial segment** (superior cervical) the nerve is situated in the maxillo-vertebro-pharyngeal space, contained in the vascular sheath of

the neck, and situated in the angle between the posterior faces of the internal carotid artery, medially and internal jugular vein, laterally.

In the **inferior cervical segment** the nerve maintains its posterior inter-veno-arterial position, but the vascular sheath of the neck becomes more thick and develops a sagittal septum (Lagenbeck) dividing it into a medial neuro-arterial compartment, that contains the primitive carotid artery and the vagus nerve, and a lateral venolymphatic compartment, that contains the internal jugular vein and the deep jugular lymphonodular chain [2].

In the **superior mediastinal segment** the vagus nerves have different right/left relations.

On the right side, the nerve passes through the thoracic inlet, crosses successively the external face of the common carotid artery, the anterior face of the right subclavian artery and the posterior face of the right venous angle. In the thymovascular segment it follows the posterior face of the superior cava vein, crosses posteriorly the azygos vein and the left bronchus and arrives on the right margin of the inter-azygo-aortic esophagus [2,5].

On the left side, the nerve passes through the thoracic inlet between the anterior face of the left subclavian artery and the posterior face of the brachiocephalic vein, then crosses anteriorly the aortic arch and laterally, the arterial ligament giving the left recurrent nerve.

The left vagus nerve passes through an adipose gliding space limited by the arterial ligament, aortic arch and left pulmonary artery, and arrives into the posterior mediastinum, on the left margin of the inter-azygo-aortic esophagus, crossing the posterior faces of the pulmonary artery and the left bronchus.

In the **inferior mediastinum**, each vagus nerve divides in 3 - 4 vertical branches with terminal appearance. The left vagus nerve branches on the anterior face of the esophagus, and the right vagus, on the posterior face. Their fibres richly anastomose and form the peri-oesophageal plexus. Above the diaphragm, the plexus fibres reunite under the peri-oesophageal adventitia into the anterior and posterior trunks that pass into the abdomen through the esophageal hiatus.

In the **abdominal segment** the vagal trunks divide into the terminal branches with different right/left distribution and territories [2,5] (table 1).

Table 1. Vagus nerve collateral and terminal branches

Vagus nerve collateral branches	Vagus nerve terminal branches
• meningeal branch (*r. meningeus*);	• anterior vagal trunk (*truncus*

• auricular branch (*r. auricularis*); • pharyngeal branch (*r. pharyngeus*); • branches for the carotid glomus (*r. sinus carotici*) (GVE); • cardiac superior and inferior branches (*rr. cardiaci cervicales superiores et inferiores*) originate from the inferior pole of the inferior ganglion and the cervical trunk, and are oriented caudally on the antero-external face of the left common carotid artery/brachiocephalic trunk upon side, and end in the anterior cardiac plexus; • superior laryngeal nerve (*n. laryngeus superior*); • internal laryngeal nerve (*r. internus*); • external laryngeal nerve (*r. externus*); • recurrent laryngeal nerve (*n. laryngeus recurrens*); • anterior pulmonary branches (*plexus pulmonalis anterior*); • posterior pulmonary branches (*plexus pulmonalis posterior*); • esophageal branches (*rr. oesophagei*).	*vagalis anterior*); • posterior vagal trunk (*truncus vagalis posterior*).

Sympathetic fibres of vagus nerve are cardioaccelerator, vasodilator and nociceptive and have been identified in the sinoatrial and atrioventricular nodes, and in the epicardium, with a higher concentration at the ventricular level [13].

2. Theoretical Background

Vagus nerve dysfunction is encountered in several cardiac diseases including atrial fibrillation (AFib) and heart failure. Increased vagal tone is a known trigger for paroxysmal AFib but the underlying mechanism is incompletely understood. Increased parasympathetic activity is supposed to enhance the acetylcholine- dependent K+-current (IKACh) implicated in the genesis of paroxysmal AFib [16].

Heart failure is characterized by an imbalance between the sympathetic (hyperstimulation) and parasympathetic (understimulation) innervation. Long term parasympathetic stimulation is associated with left ventricular remodelling, myocyte apoptosis, fibrosis and electrical instability. As pharmacological interventions that increase parasympathetic tone, limited nervous stimulation (baroreceptor activation, spinal cord and vagus nerve stimulation) has been proposed [1,14].

Vagus nerve stimulation (VNS) may slow or cancel these processes by inhibiting the renin-angiotensin system and TNF-α, IL-1, IL-6, IL-18 liberation (anti-inflammatory action) [3].

The first studies concerning the effects of chronic VNS on heart failure were performed on dogs and lab rats after inducing heart failure by myocardial infarction [8,15]. Li et al. stimulated the vagus nerve in lab rats until obtaining a diminishment of the heart rate by 20-30 beats/minute (resting heart rate 360 beats/minute). Left ventricular ejection fraction (LVEF) improved and mortality rate at 140 days decreased from 50% to 14% [8]. Similar results were obtained by Vanoli et al. in a study carried out on canine subjects [15].

In humans, VNS was first approved for drug-resistant depression and epilepsy treatment [10,12]. In 2008 there was developed the first vagus nerve stimulator for chronic heart failure (CardioFit) and tested in a pilot study performed by Schwartz et al. on 8 patients with encouraging results (NYHA class improvement, reduction of left ventricular end-systolic volume) [11].

3. Argument of the paper

The aim of the current study was to perform a meta-analysis of the available data obtained in a clinical setting for VNS in heart failure patients in order to establish a potential benefit in terms of cardiac function.

4. Material and methods

The authors performed a systematic review and meta-analysis of available data published between January 2010 - April 2017 by searching the Medline database using "vagus nerve stimulation" and "heart failure" as keywords. Selection criteria for identified studies included any randomised or non-randomised research on the effect of vagal nerve stimulation (VNS) in human patients with cardiac failure no matter the stimulation parameters

or presence of cardiac sensing. From 116 identified studies, only 4 met the inclusion criteria after abstract analysis.

In the same time, the authors analysed the applicability of this procedure on 401 patients with AFib enrolled between 2012-2017 in the project *Extension and Modernisation of a Research Centre for the Invasive Treatment of Atrial Fibrillation as a Method for Preventing Heart Failure, by Expanding the Research-Development Infrastructure of the Cardiovascular Diseases Institute "Prof. Dr. G.I.M. Georgescu Iasi"* (financed by POS CCE - 2nd axis, SMIS-CSNR code 13970, ID no. 872, contract no. 262/28.09.2010) further called *CCTIFA*.

5. Results

The four identified studies (2 randomized, 2 non-randomized) evaluated the effect of VNS in patients ≥18 years-old with NYHA functional class II-III heart failure due to various causes and reduced left ventricular ejection fraction (LVEF) [3,4,6,7,9,17].

The VNS procedure involved stimulating the vagus nerve in the cervical region through an electrode attached to a stimulator placed in a subcutaneous pectoral pocket or in the subclavicular space with or without intracardiac sensing through another electrode (interventional cardiology) placed in the right ventricle for detecting the heart rate. Stimulation parameters are generally adjusted gradually to levels that trigger mild side effects such as cough (expiratory reflex), neck pain or heart rate reduction and then slightly diminished to ensure tolerance.

The comparison of the 4 major studies is detailed in table 2.

Table 2. Comparison of major studies concerning vagal nerve stimulation

	De Ferrari et al. (7)	**INOVATE-HF** (14,15)	**ANTHEM-HF** (16,17)	**NECTAR-HF** (13)
Study type	Non-randomized	Randomized in a 3:2 ratio	Non-randomized	Randomized in a 2:1 block permuted
Stimulator	**Cardiofit**, BioControl Medical	**Cardiofit**, BioControl Medical	**Demipulse Model 103 pulse generator and PerenniaFLEX Model 304 Lead,** Cyberonics	**Precision**, Boston Scientific
Electrodes	Helical bipolar electrode	Helical bipolar electrode	Helical bipolar electrode	Helical bipolar electrode
Stimulation	Intermittent	Fixed time	Intermittent	20Hz

protocol	pulsations (2s ON, 6s OFF) Maximum 5.5 mA Duty cycle: max. 25%	period after the R wave Maximum 5.5 mA Duty cycle: 25%	10Hz 250μsec pulsations Maximum 3.0 mA Duty cycle: 17.5%	Maximum 4 mA Duty cycle: 12.5%
Cardiac sensing	Yes	Yes	No	No
Number of patients (VNS)	32	436	60	87
Inclusion criteria	NYHA functional class II-III Sinus rhythm 60-110 bpm LVEF ≤35% 6 minutes' walk test	NYHA functional class III Sinus rhythm 65-110 bpm QRS <120 ms LVEF <40% LVEDD 50-80 mm	NYHA functional class II-III QRS ≤150ms LVEF ≤40% LVEDD 50-80 mm	NYHA functional class II-III LVEF ≤35% LVEDD ≥55 mm
Comparison group	None	Standard optimal medical therapy	Baseline values	6 months randomized and controlled phase (stimulation turned OFF)
Endpoints	Adverse effects	Heart failure hospitalization and all-cause mortality	Incidence of procedure and device-related adverse events, LVEF and LVESV	LVESD from baseline
Time interval for evaluation of all patients	3, 6 months	6 months 12 months	6 months	6 months
Result	40.6% adverse effects – 6.2% related to the procedure NYHA functional class improvement 59%	Heart failure hospitalization 30.3% VNS vs. 25.8% control (n.s.) Annual mortality rates 9.3% vs. 7.1% (n.s.)	No significant adverse effects (one related to the therapy) 4.5% LVEF improvement LVESV no statistical significant	LVESD -0.04 cm therapy group vs. -0.08 cm control group (n.s.)

	6 minutes' walk test – 60 m increase LVEF improvement 7%		improvement HR reduction 8 bpm 6 minutes' walk test – 56 m increase NYHA functional class improvement 77%	
Limits	Small sample Pilot study	Narrow spectrum of inclusion criteria Approximate probabilities Learning curve	Small study group Non-randomised Unicentric Non-Caucasian population (India) Influence of stimulation side	Study design (ON/OFF) On-going trial Lack of concurrent control group after 6 months Possible inappropriate patient selection
Conclusion	Safe and tolerable, may improve quality of life and left ventricular function	No reduction in heart failure hospitalization or death rates	Cardiac functional status and symptomatic improvement	No effect on primary endpoint

*LVEF - left ventricular ejection fraction, LVESD – left ventricular end-systolic diameter, LVEDD – left ventricular end-diastolic diameter, LVESV – left ventricular end-systolic volume

NECTAR-HF and INOVATE-HF failed to demonstrate a significant improvement of mortality rate, functional remodelling or functional capacity in symptomatic heart failure patients (13-15). De Ferrari et al. and ANTHEM-HF signalled a LVEF improvement (7% vs. 4.5%), left ventricular end-systolic volume diminishment (14 mL vs. 4.1 mL), six-minute walk distance increase (60 m vs. 56 m), and NYHA functional class improvement in 59% and 77% of cases respectively [3,4,9]. ANTHEM-HF also indicated a reduction of the left ventricular end-systolic diameter by 1.7 mm [4,9].

At the Cardiovascular Diseases Institute (Iasi, Romania), 401 patients with AFib were enrolled between 2012-2017 in the project *CCTIFA*. Of these patients, 155 (38.65%) were diagnosed with neurogenic AFib, 91 vagally mediated paroxysmal AFib (22.69%) and 64 (15.96%) with adrenergic AFib. 274 patients (68.33%) with AFib presented heart failure, mostly NYHA functional class II (254 patients, 75 with vagally mediated paroxysmal AFib), followed by NYHA functional class III (18 patients, none with vagally mediated paroxysmal AFib) and IV (2 patients, none with vagally mediated paroxysmal AFib). Except the 75 cases with vagally mediated paroxysmal AFib, the rest of 199 patients with NYHA class II-IV heart failure and AFib could have been considered eligible for vagus nerve stimulation but as the above mentioned internationally acknowledged randomized trials published after project implementation (specifically, between 2013-2016) failed to demonstrate an objective and significant benefit, the investment and risk have been considered unjustified at the moment.

6. Discussions

In the heart, right vagus nerve fibres distribute mainly to the sinoatrial node and their stimulation decreases the heart rate compared to left vagus nerve fibres that distribute to the atrioventricular node and His bundle, their stimulation inducing an atrioventricular block. Atria have a rich parasympathetic cholinergic innervation compared to the ventricles and coronary arteries [13].

Cardiac sympathetic innervation is controlled by caudal ventrolateral medulla centres through incompletely elucidated mechanisms. Superior, middle and inferior cardiac nerves originate in paravertebral ganglia of the cervical (superior, middle and inferior) and upper thoracic (T1-T5) region. Left branches of all three cardiac nerves contribute to the formation of the preaortic plexus (superficial cardiac plexus) compared to right branches that contribute to the formation of the retroaortic plexus (deep cardiac plexus) [13].

Superior cardiac parasympathetic nerve (*Rami cardiaci superiores*) originates in the inferior ganglion of the vagus nerve (plexiform ganglion) or in the superior laryngeal nerve. The nerve anastomoses with the sympathetic cardiac fibres, the right one ending in the deep cardiac plexus and the left one in the superficial cardiac plexus. The middle cardiac parasympathetic nerve originates in the recurrent laryngeal nerve and ends similarly to the superior. The right inferior cardiac parasympathetic nerve (*Rami cardiaci*

inferiores) originates 1-2 cm below the origin of the recurrent laryngeal nerve and distributes to the pulmonary and deep cardiac plexus. The left inferior parasympathetic nerve originates in the recurrent laryngeal nerve and divides in two branches, one anterior ending in the pulmonary and superficial cardiac plexus and one posterior ending in the deep cardiac plexus [13].

The imbalance between sympathetic activity and parasympathetic tone has long time been considered a potential contributor to the progression of heart failure. Experimental models and small non-randomized clinical studies have suggested that increased parasympathetic tone through direct VNS may increase the quality of life, improve the cardiac function (NYHA class), reverse left ventricular remodelling, reduce inflammation and mortality rates. The cardiovascular deleterious effects of VNS are minimal and represented by mild bradycardia and negative inotropic action preventable by titration in small increments (0.25 mA).

NECTAR-HF and INOVATE-HF, randomized studies performed on the largest groups, failed to demonstrate a clear benefit of VNS in heart failure in terms of LVEF, LVEDD or LVEDV but proved the safety of the technique than can be performed with a low complications rate [6,7,17]. De Ferrari et al. and ANTHEM-HF indicated a functional benefit that could be subjective in nature given the absence of patient blindness regarding the treatment, the fact that some patients were able to sense the stimulation (Placebo effect), and the small study groups [3,4,9].

Among the possible explanations for the absence of positive results of NECTAR-HF and INOVATE-HF trials could be the unknown ideal stimulation site, non-standardized stimulation parameters (subject to probing), unknown optimal stimulation duration and limited follow-up duration [6,7,17].

The four papers analysed use different study designs, stimulators, electrodes and stimulation protocols in relation to different outcomes. The stimulation electrode was placed on the right or left vagus nerve in the cervical region but the type of stimulated fibres is unknown. The short stimulation and follow-up periods could be associated to an incomplete therapeutic effect of VNS with induced small or no differences between VNS and standard optimal medical therapy. Also, when affirming results, the researchers compare the endpoint parameters to different references (baseline parameters, control group with optimal medical therapy, same patients with interrupted stimulation – "OF").

The unfavourable results of the NECTAR-HF and INOVATE-HF trials should not discourage further research as there is a known autonomic nervous system imbalance associated to heart failure. Prior to further clinical studies, the specific site, intensity and duration of adequate stimulation

should be identified together with a method of isolating the efferent vagal fibres in order to avoid cross-stimulation and side-effects.

7. Conclusions

In conclusion, despite encouraging experimental and simulation data, randomized studies failed to demonstrate a clear clinical benefit of VNS in terms of cardiac remodelling, functional capacity and mortality in patients with heart failure and reduced LVEF. The observed benefits in quality of life have to be interpreted with caution given their subjective nature as patient blindness was obtained only in the NECTAR-HF (ON/OFF study). Prior to new clinical studies, the specific site, intensity and duration of adequate stimulation should be identified together with a method of isolating the efferent vagal fibres in order to avoid cross-stimulation and side-effects.

8. Funding

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